Supplementary Information

Experimental section

Materials and instruments

Commercially obtained chemicals and solvents were used without further purification. *N*–Phthaloylglycine, Nickel(II) nitrate, Copper(II) nitrate and Zinc(II) perchlorate, 1,2–diaminocyclohexane, ethidium bromide (EB), tris–(hydroxymethyl)aminomethane (tris buffer) were purchased from Sigma Aldrich. The supercoiled pBR322 plasmid DNA (Genei) and 6x loading dye (Fermentas Life Science) were utilized as received. The disodium salt of ct–DNA were purchased from Sigma Chemicals Co. and stored at 4 °C. Experiments involving the interaction studies of the complexes with ct–DNA were carried out in aqueous–saline Tris–buffer solution (pH=7.4). The concentration per base pairs for both ct–DNA was determined spectrophotometrically by considering ε260 nm values to be 6600 and 7700 $M^{-1}cm^{-1}$, respectively. Elemental analysis was carried out on Carlo Erba Analyser Model 1106. Fourier–Transform infrared (FT–IR) spectra were recorded on spectrum Two (Perkin Elmer) FT–IR spectrometer. The EPR spectra of the copper complexes were recorded on a Varian E 112 EPR spectrometer using X–band frequency (9.5 GHz) at room temperature. Molar conductance was measured at room temperature on a Eutech con 510 electronic conductivity bridge. Electronic spectra were recorded on UV–1700 PharmaSpec UV–vis spectrophotometer. Thermogravimetric analysis (TGA) was carried out in dynamic nitrogen atmosphere with a heating rate of $20^{\circ}Cmin^{-1}$ using Shimadzu TA−60 WS thermal analyzer. ESI–MS spectra were recorded on Micromass Quattro II triple quadrupole mass spectrometer. Emission spectra were made on Shimadzu RF–5301PC Spectrofluorophotometer. ^{1}H NMR spectra were obtained on a JEOL–400YH spectrometer at 400 MHz, with Me2SO–d6 as solvent. Cleavage experiments

were performed with the help of Axygen electrophoresis supported by Genei power supply (50–500 V) and photographed by Vilber–INFINITY gel documentation system.

Synthesis of complex 1

Complex **1** was synthesized by reacting 2 mmol (0.410 g) of *N*–Phthaloylglycine with 2 mmol (0.228 g) of 1,2–diaminocyclohexane and 1 mmol (0.241 g) of copper(II) nitrate trihydrate in methanol at room temperature for 4 hours. The resulting solution was filtered and kept aside for slow evaporation at room temperature. Light blue crystals were collected after 3 days which were soluble in organic solvents like H_2O, MeOH, DMF and DMSO.

Yield: 83%, melting point: 254 ^oC, CCDC = 2130104, Elemental analysis calculated for $[C_{32}H_{48}N_6NiO_{12}]$: calc. C, 48.46; H, 7.39; N, 12.84. Found: C, 48.56; H, 7.38; N, 12.86. FT-IR (KBr, υ_{max}/cm^{-1}): 2937 υ(C–H), 1713 υ(C=O), 553 υ(M−O), 414 υ(M−N), 3328 υ(N-H). UV−vis (λ_{max}, nm) in DMSO: 248 nm (π−π*), 315 (n−π*), 725 nm (d−d).

Synthesis of complex 2

Complex **2** was synthesized by the reaction of 2 mmol (0.410 g) *N*-Phthaloylglycine with 2 mmol (0.228 g) of 1,2-diaminocyclohexane and 1 mmol (0.241 g) of copper(II) nitrate trihydrate at room temperature for 4 hours. The resulting reaction mixture was filtered and allowed to evaporate slowly at room temperature. Needle-like blue crystals suitable for single X-ray diffraction were obtained in bulk after 3 days of slow evaporation of the reaction mixture. The crystals were found to be stable towards air and soluble in solvents like H_2O, DMSO and DMF.

Yield: 74%, melting point: 273 ^oC, CCDC = 2126710, Elemental analysis calculated for $[C_{32}H_{40}CuN_6O_8]$: calc. C, 53.26; H, 6.91; N, 14.12. Found: C, 53.33; H, 6.95, N, 14.18. FT–IR (KBr,υ_{max}/cm^{-1}): 2932 υ(C–H), 1708 υ(C=O), 425 υ(M–N) and 3305 υ(N-H). UV-vis (λ_{max}, nm) in DMSO: 265 (π−π*), 308 (n−π*), 761 nm (d−d).

Synthesis of complex 3

Complex **3** was synthesized by stirring methanolic solutions of *N*-Phthaloylglycine (0.205 g, 1 mmol), copper(II) nitrate trihydrate (0.241 g, 1 mmol) and 1, 2-diaminocyclohexane (0.228 g, 2 mmol) at room temperature for 3 hours. The resulting solution was filtered and colourless needle like crystals were obtained after 4 days upon slow evaporation of solvent at room temperature.

Yield: 79%, melting point: 268 ^{o}C. CCDC = 2128796, Elemental analysis calculated for [$C_{32}H_{48}N_6ZnO_{12}$]: C, 47.87; H, 7.30; N, 12.69; found C, 47.81; H, 7.38; N, 12.73. FT-IR (KBr, υ_{max}/cm^{-1}): 2938 υ(C–H), 1713 υ(C=O), 577 υ(M–O), 414.79 υ(M–N) and 3329 υ(N–H). UV-vis (λ_{max}, nm) in DMSO: 246 (π−π*), 308 (n−π*).

X-ray crystallography

Single crystal X-ray diffraction studies of complexes (**1**-**3**) were performed on a D8 VENTURE Bruker AXS diffractometer employing graphite mono–chromated Mo–Kα radiation generated from a fine focus sealed tube (λ=0.71073 Å) at 150 K. The structures were solved by dual space algorithm using the SHELXT program and further refined with full matrix least square methods based on F2 (SHELXL). All non–hydrogen atoms were refined with anisotropic atomic displacement parameters. Hydrogen atoms were finally included in their calculated position. The drawings of the complexes were realized with PLATON.

Density Functional Theory (DFT) Studies

The computational studies were carried out by employing ORCA 3.0.1 software to perform geometry optimization of by hybrid B3LYP38 functional using Aldrich's def2–TZVP basis set for nickel, copper and zinc atoms and def2–SVP basis set for other non–metal (C,H,O,N) atoms. The initial files for geometry optimization were obtained from the X–ray crystallographic data

which were further utilized to obtain HOMO and LUMO orbitals. The resolution of identity (RI) approximation with decontracted auxiliary def2–SVP/J and def2–TZV/J Coulomb fitting basis as well as chain of spheres (RIJCOSX) approximation were utilized to exact exchange as implemented in ORCA. Contour plots of molecular orbitals of the complexes were generated using Avagadro software.

Binding studies with ct–DNA

Interaction studies with ct–DNA were carried by employing absorption titration and FID assay, according to the standard methods previously adopted by our laboratory.

pBR322 cleavage studies

The ability of the complexes to bring about DNA strand scission was assayed by gel electrophoresis through monitoring the conversion of supercoiled form (Form I) to nicked circular (Form II) which is further cleaved into linearized form (Form III) on applying an electric field. The cleavage experiments of supercoiled pBR322 DNA (300ng) in aqueous–saline Tris–buffer buffer at pH 7.5 were carried out using Agarose gel electrophoresis. The samples were incubated at 37 °C for 45 min and the cleavage activity was monitored in the absence and presence of additives to study the mechanistic aspect of the cleavage pathway.

Cytotoxic studies

In vitro antitumor screening of complexes **1**–**3** was performed on human cancer lines of two different histological origin viz., HepG2 and PTEN–caP8. The effect of complexes **1–3** on cell viability was determined by MTT assay. Briefly, cells were seeded in 96-well dishes at a density of 3.5×10^3 cells per well. Cells were allowed to attach for 24h before incubation with fresh

medium containing either complex **1**/**2**/**3** (2.5-10.0 mM) for 48h. After incubation for 48h at 37 ^{o}C, MTT assay was performed as described previously

Molecular docking studies

The molecular docking studies were performed by employing HEX 8.0 software. The B-DNA dodecamer d(CGCGAATTCGCG)$_2$ (PDB ID: 1BNA) crystal structure was downloaded from the http://www.rcsb.org./pdb (protein data bank). Before employing docking experiments, the structure of complexes **1-3** were converted into PDB format and the visualization was done by using Discovery Studio molecular graphics program.

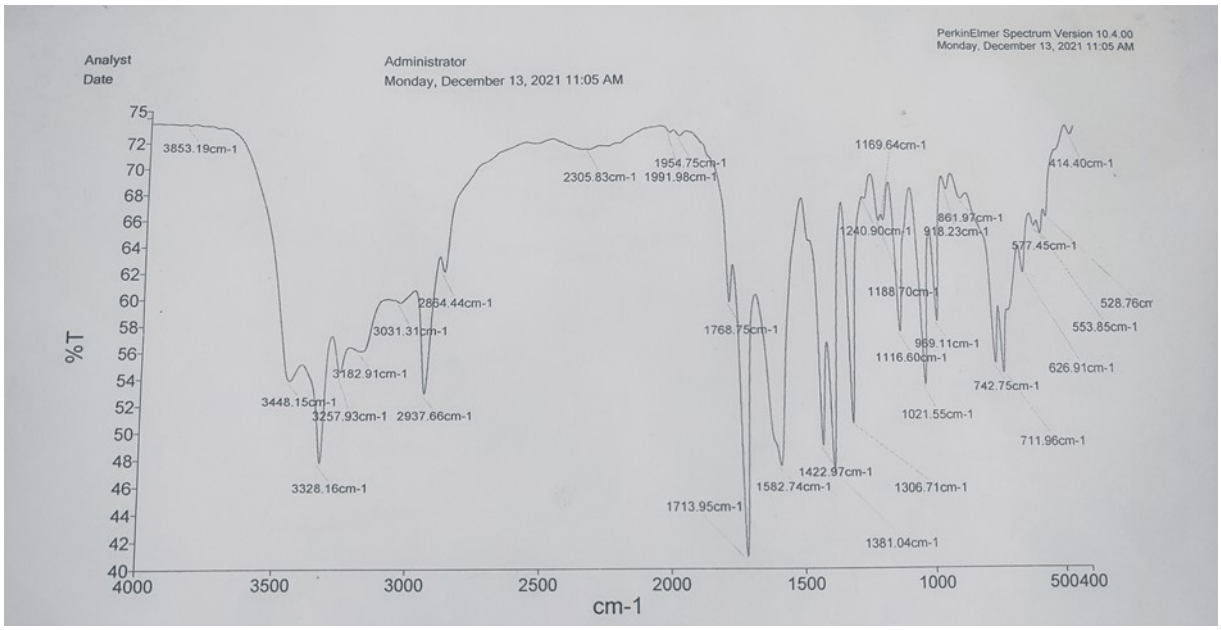

Fig. S1. FT–IR spectra of complex **1**.

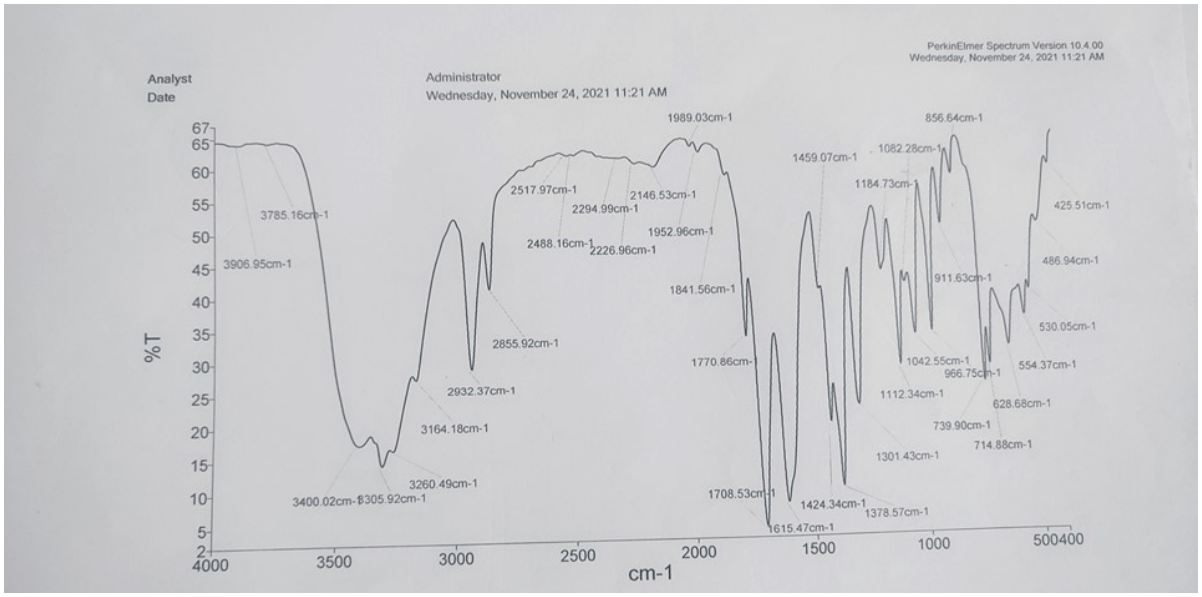

Fig.S2. FT–IR spectra of complex **2**.

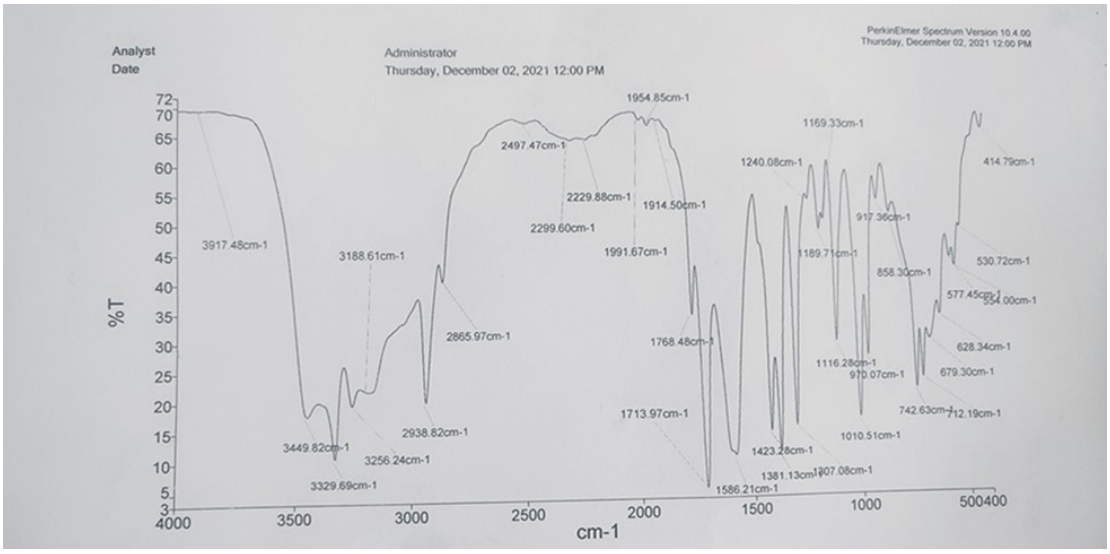

Fig.S3. FT–IR of complex **3**.

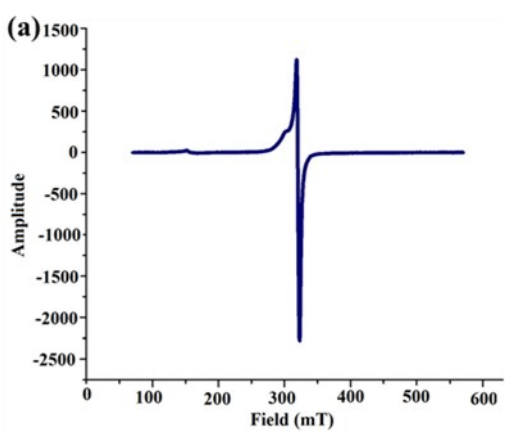

Fig. S4. EPR spectra of complex **2**.

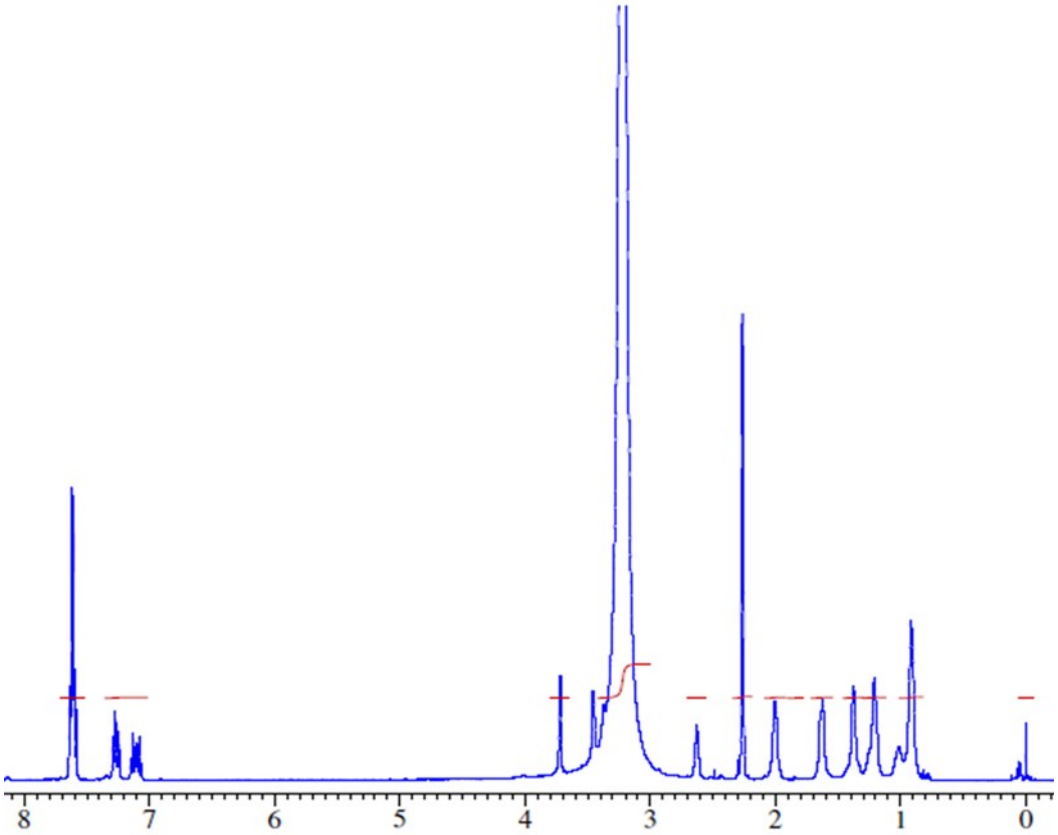

Fig.S5. ^{1}H NMR spectrum of complex **1**.

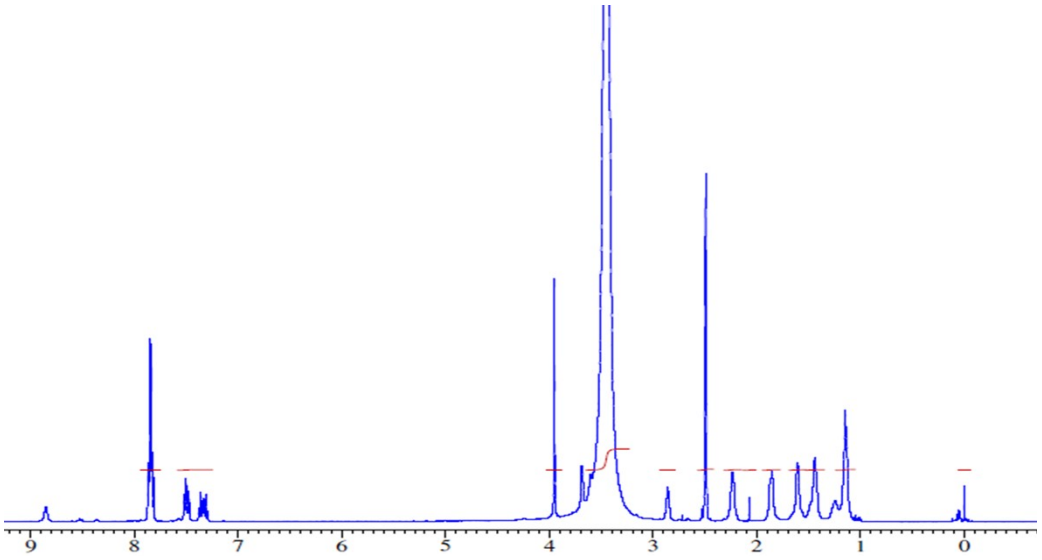

Fig.S6. ^{1}H NMR spectrum of complex **3**.

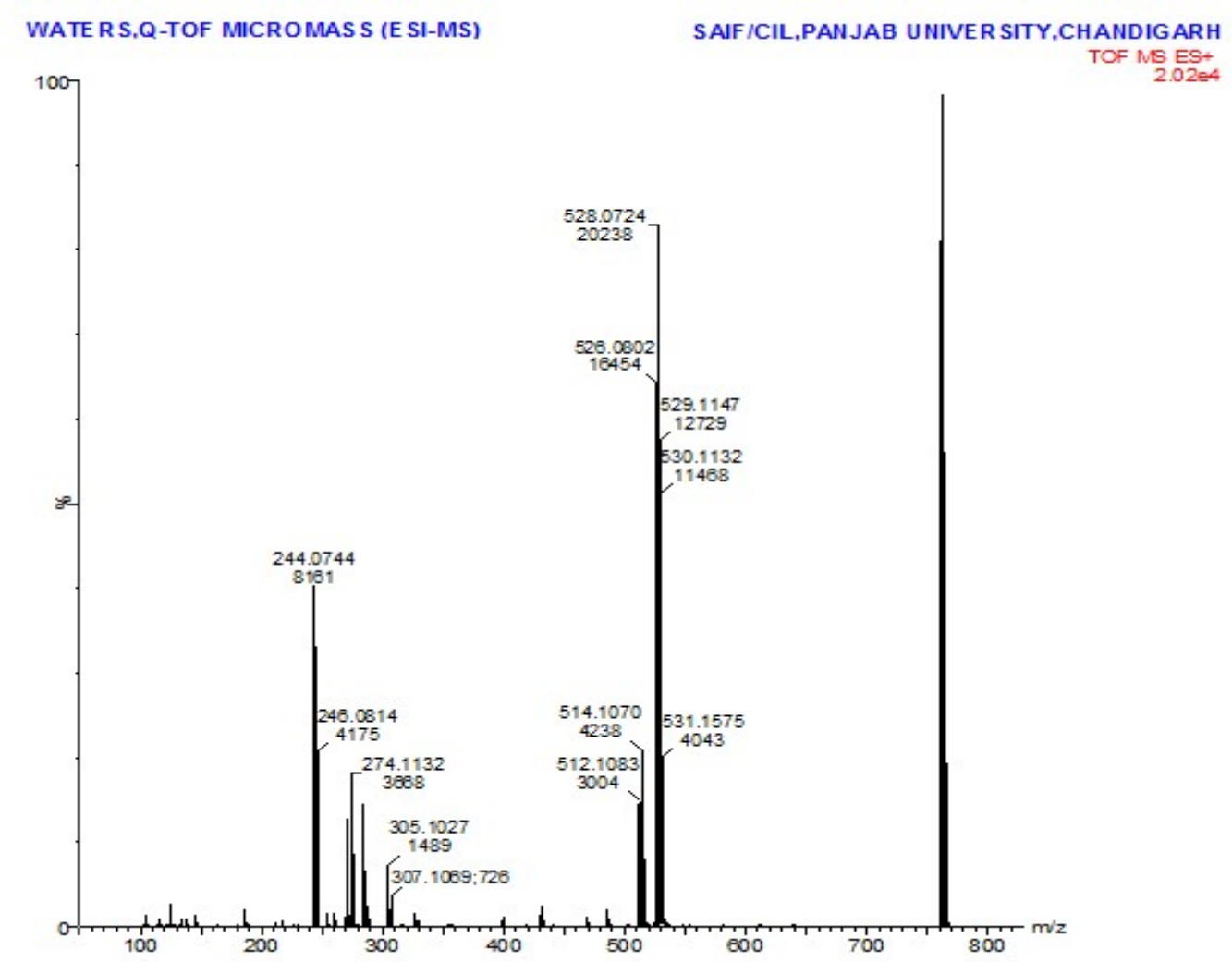

Fig.S7. ESI–MS of complex **1**.

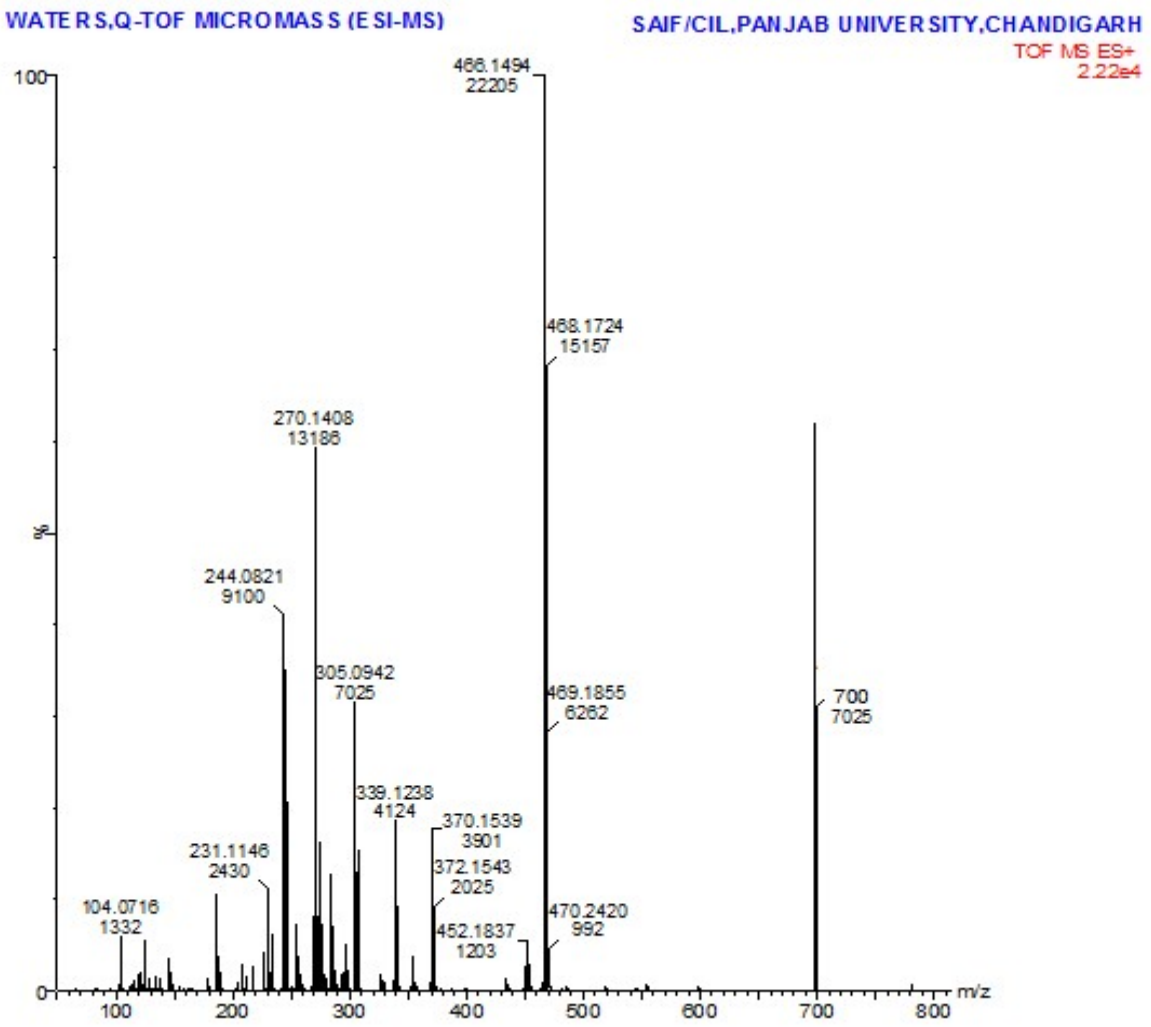

Fig.S8. ESI–MS of complex **2**.

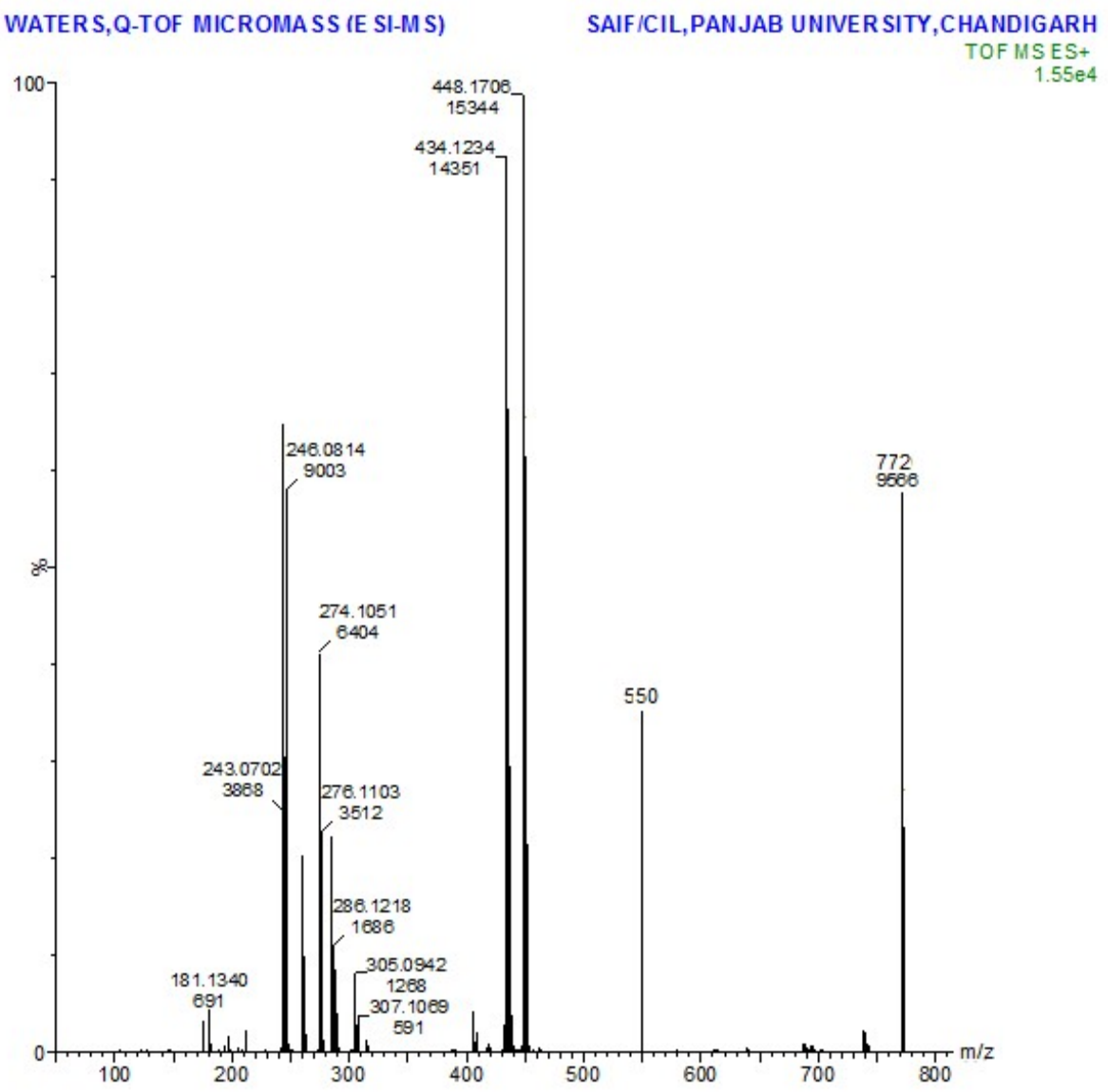

Fig.S9. ESI–MS of complex **3**.

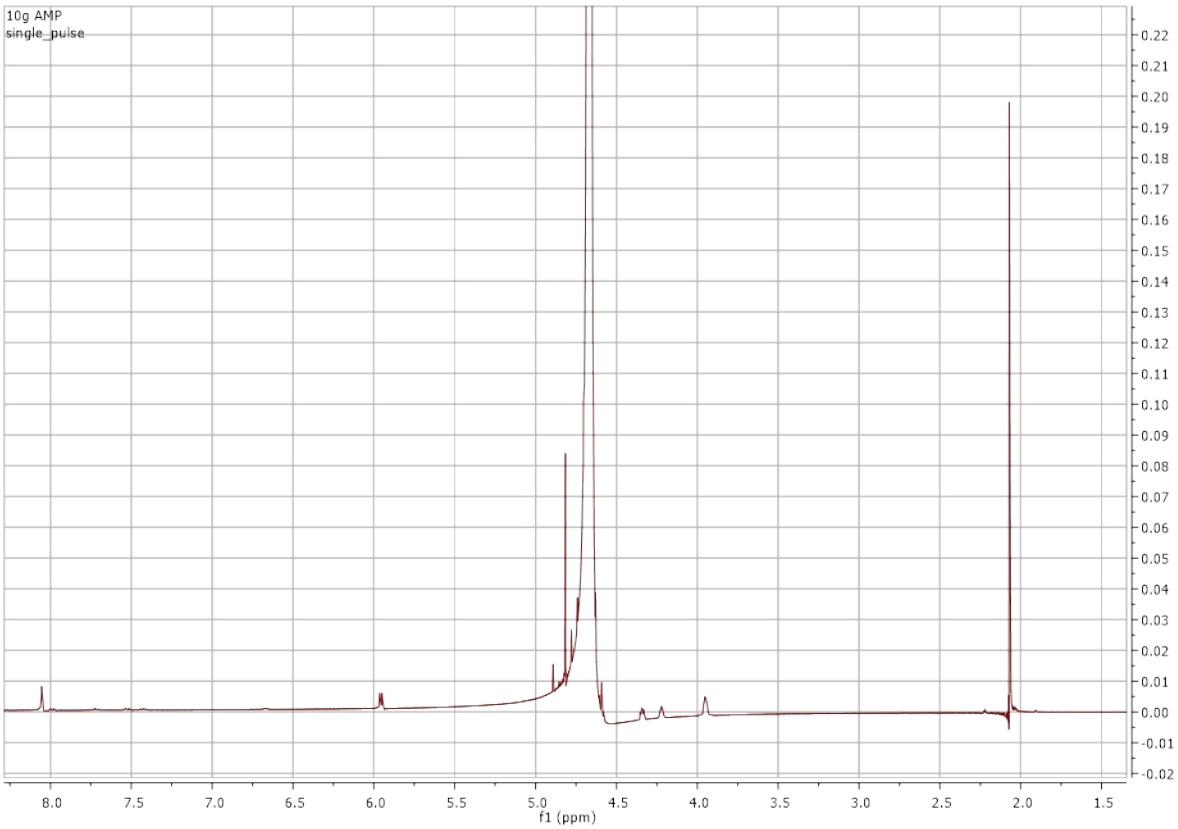

Fig.S10. ^{1}H NMR of nucleotide AMP.

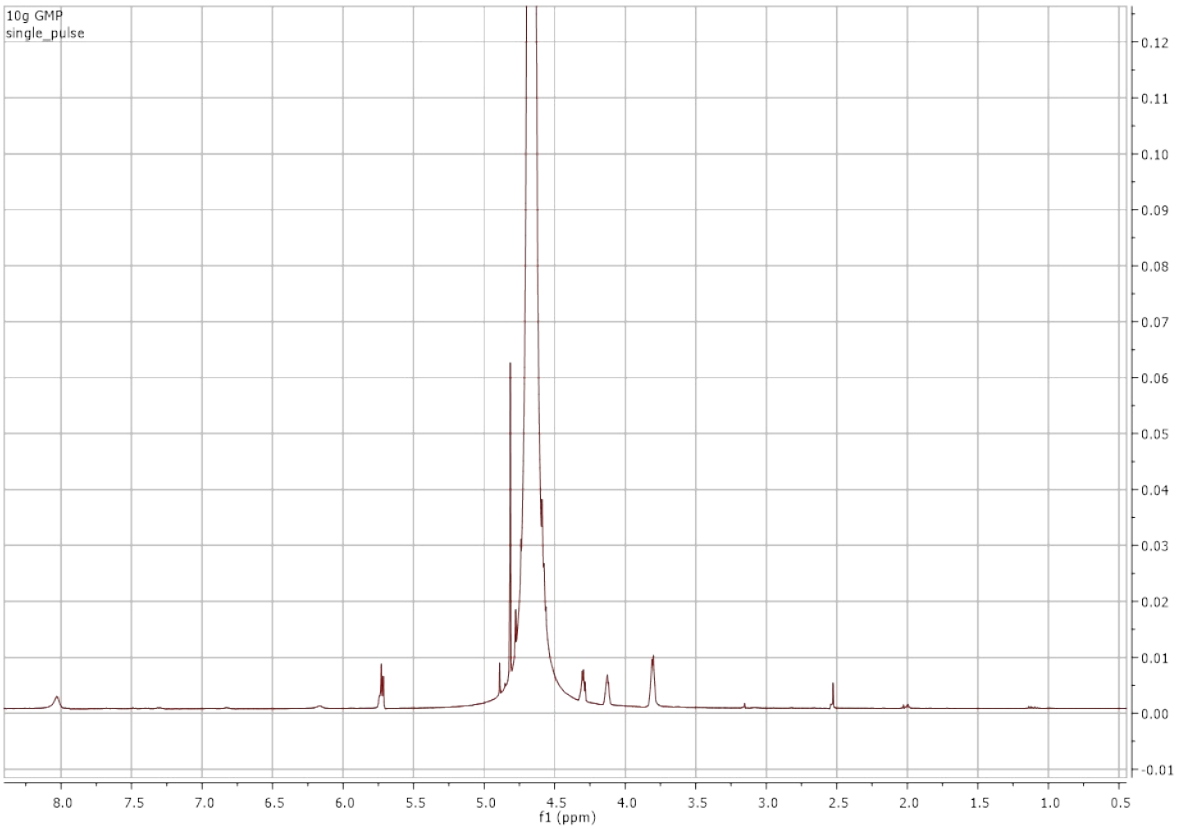

Fig.S11. ^{1}H NMR of nucleotide GMP.

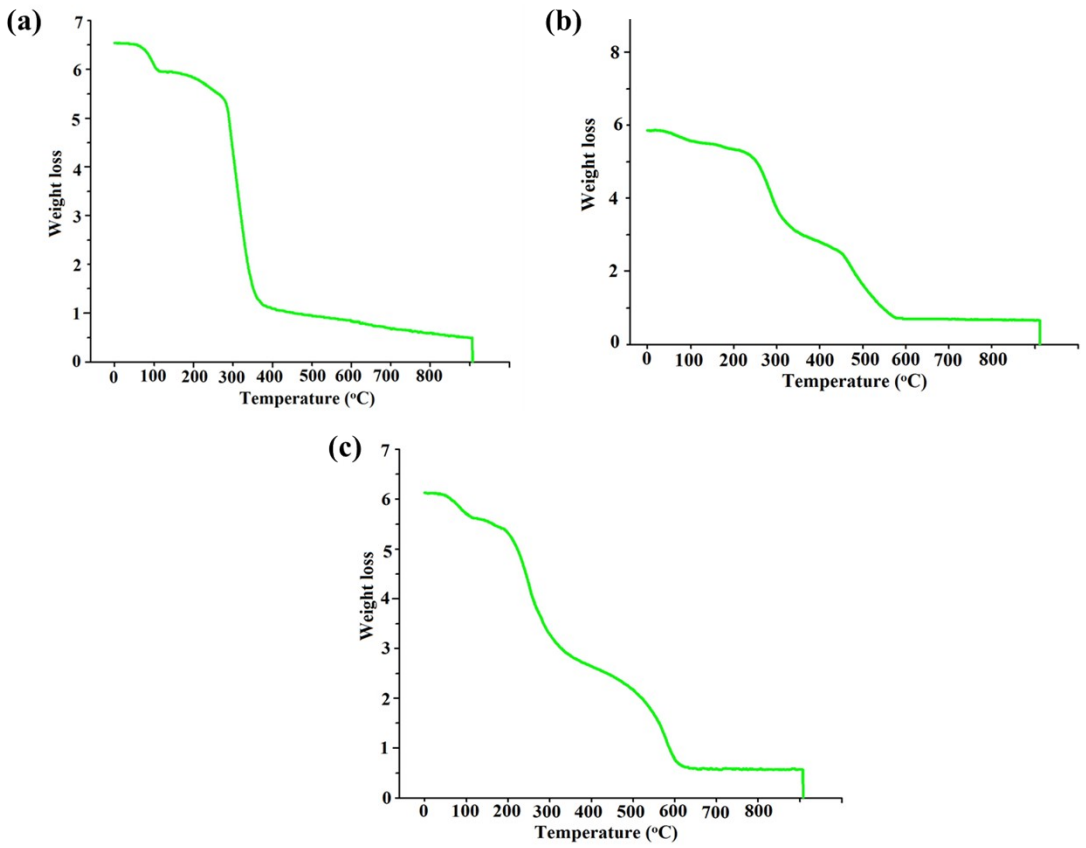

Fig. S12. Thermogravimetric analysis of complexes (a) **1**, (b) **2** and (c) **3**.

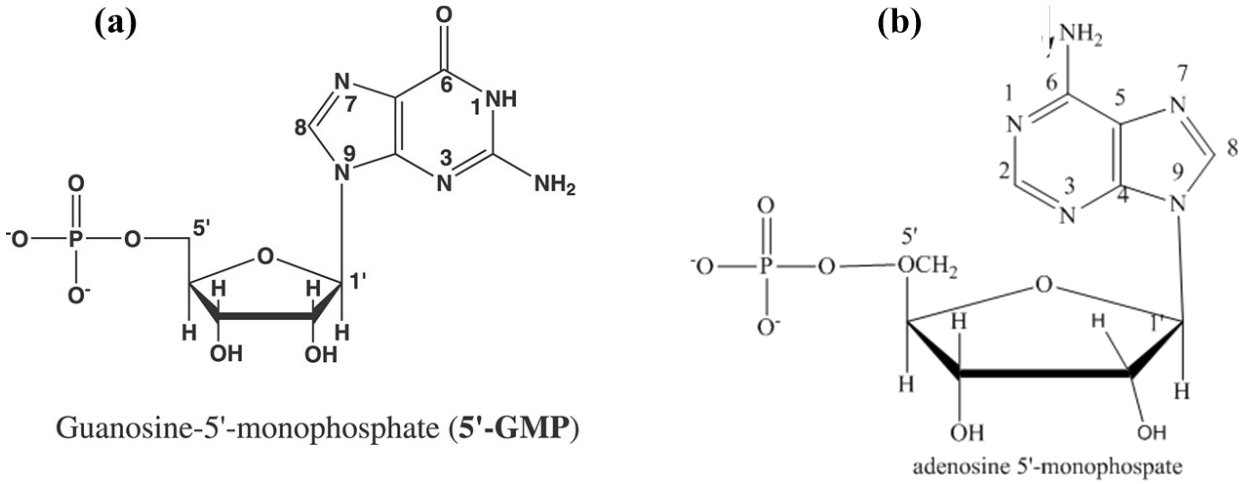

Fig. S13. Structures of (a) Guanosine-5’-monophosphate and (b) Adenosine-5’-monophosphate.